Human cytomegalovirus infection of human embryonic stem cell-derived primitive neural stem cells is restricted at several steps but leads to the persistence of viral DNA.

Journal: J Virol

Publication Year: 2014

Authors: Jean-Philippe Belzile, Thomas J Stark, Gene W Yeo, Deborah H Spector

PubMed link: 24453373

Funding Grants: Viral-host interactions affecting neural differentiation of human progenitors

Public Summary:
Human cytomegalovirus (HCMV) is a betaherpesvirus that is highly prevalent in the population. HCMV infection is usually asymptomatic but can lead to severe consequences in immunosuppressed individuals. HCMV is also the most important infectious cause of congenital developmental birth defects. Manifestations of fetal HCMV disease range from deafness and learning disabilities to more severe symptoms such as microcephaly. In this study, we have used embryonic stem cells to generate primitive neural stem cells and have used these to model HCMV infection of the fetal central nervous system (CNS) in vitro. Our results reveal that these cells, which are similar to those present in the developing neural tube, do not support viral replication but instead likely constitute a viral reservoir. Future work will define the effect of viral persistence on cellular functions as well as the exogenous signals leading to the reactivation of viral replication in the CNS.

Scientific Abstract:
Congenital human cytomegalovirus (HCMV) infection is a major cause of central nervous system structural anomalies and sensory impairments. It is likely that the stage of fetal development, as well as the state of differentiation of susceptible cells at the time of infection, affects the severity of the disease. We used human embryonic stem (ES) cell-derived primitive prerosette neural stem cells (pNSCs) and neural progenitor cells (NPCs) maintained in chemically defined conditions to study HCMV replication in cells at the early stages of neural development. In contrast to what was observed previously using fetus-derived NPCs, infection of ES cell-derived pNSCs with HCMV was nonprogressive. At a low multiplicity of infection, we observed only a small percentage of cells expressing immediate-early genes (IE) and early genes. IE expression was found to be restricted to cells negative for the anterior marker FORSE-1, and treatment of pNSCs with retinoic acid restored IE expression. Differentiation of pNSCs into NPCs restored IE expression but not the transactivation of early genes. Virions produced in NPCs and pNSCs were exclusively cell associated and were mostly non-neural tropic. Finally, we found that viral genomes could persist in pNSC cultures for up to a month after infection despite the absence of detectable IE expression by immunofluorescence, and infectious virus could be produced upon differentiation of pNSCs to neurons. In conclusion, our results highlight the complex array of hurdles that HCMV must overcome in order to infect primitive neural stem cells and suggest that these cells might act as a reservoir for the virus. IMPORTANCE: Human cytomegalovirus (HCMV) is a betaherpesvirus that is highly prevalent in the population. HCMV infection is usually asymptomatic but can lead to severe consequences in immunosuppressed individuals. HCMV is also the most important infectious cause of congenital developmental birth defects. Manifestations of fetal HCMV disease range from deafness and learning disabilities to more severe symptoms such as microcephaly. In this study, we have used embryonic stem cells to generate primitive neural stem cells and have used these to model HCMV infection of the fetal central nervous system (CNS) in vitro. Our results reveal that these cells, which are similar to those present in the developing neural tube, do not support viral replication but instead likely constitute a viral reservoir. Future work will define the effect of viral persistence on cellular functions as well as the exogenous signals leading to the reactivation of viral replication in the CNS.